**Editorial**

**Oral Cancer Chemotherapy: The Promise and the Pitfalls**

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The future for oral cancer chemotherapy has never been brighter. The need to move cancer treatment from a predominantly hospital-based, inpatient system into the ambulatory setting has joined with the growing body of information demonstrating higher antitumor activity, lower systemic toxicity, or both with dosing regimens that produce prolonged exposure to some cancer chemotherapy. This has led to further exploration of oral administration of anticancer drugs that have been available for many years (e.g., etoposide, cyclophosphamide, and idarubicin) and novel strategies for oral use of anticancer drugs traditionally administered by the i.v. route (paclitaxel plus cyclophosphamide, 5-fluorouracil plus eniluracil), leading to a new era in the administration of cancer chemotherapy (1).

The promise for oral chemotherapy is well illustrated by the use of mercaptopurine in maintenance therapy for childhood acute lymphoblastic leukemia. The daily administration of oral mercaptopurine during many weeks of continuation therapy is an important component of most treatment protocols for childhood acute lymphoblastic leukemia (2, 3), and this schedule could not be conveniently achieved with i.v. therapy. Oral cyclophosphamide has been an important component of adjuvant therapy for breast cancer for over a decade, permitting self-administration in a convenient setting and allowing patients to have a greater role in their therapy. With the development of oral anthracyclines (such as idarubicin) and less variable approaches for oral 5-fluorouracil administration (such as coadministration with eniluracil), treatment regimens with only oral chemotherapy are now under clinical evaluation for adjuvant breast cancer (4).

The significant schedule dependency of etoposide, 5-fluorouracil, topoisomerase I inhibitors, and other classes of chemotherapy represent areas in which chronic oral administration of chemotherapy may make a significant difference for patients with cancer. Many of the pitfalls of oral chemotherapy can be anticipated from well-documented experiences with other therapeutic agents, including variable absorption, unpredictable and incomplete bioavailability, and uncertainty about patient compliance. Nearly all medications demonstrate a high degree of variation in oral bioavailability among patients. The report by Hande et al. (5) in this issue of *Clinical Cancer Research* highlights this problem. Inter- and intrapatient variability in etosposide area under the curve were evaluated using an elegant stable isotope dilution method that allowed simultaneous administration of i.v. and oral medication. The investigators were able to demonstrate that intrapatient variation in i.v. etoposide (<10%), was much less than the 22.2% intrapatient coefficient of variation observed after oral etoposide administration. The large intrapatient variability observed with oral administration is similar to that seen with other medications that undergo a significant amount of metabolism by small bowel and/or hepatic P-450 enzymes. Not surprisingly, a greater degree of interpatient variability (2–3-fold), compared with intrapatient variability, was observed after both i.v. and oral administration of etoposide.

The report makes two points with broad implications for the development of oral chemotherapy:

(a) The administration of repeated doses of a drug to the same patient will have less pharmacokinetic variation than that observed in the overall patient population. This is not unanticipated, because genetic sources of variability are eliminated when comparisons are made within the same individual. The lower intrapatient variability suggests that approaches such as individualized therapy based on measurement of drug concentrations in blood (therapeutic drug monitoring) or titration of the dose based on toxicity may be achievable within patients by measuring concentrations early in therapy and using this information to determine future doses. However, the assumption that less variability in pharmacokinetics will lead to less variation in toxicity is not supported by the literature for all drugs (6).

(b) A second point from the paper by Hande et al. (5) is that greater variability in plasma pharmacokinetics should be expected with oral administration when compared with i.v. administration of cancer chemotherapy, as is widely recognized for other classes of medication. This has important implications for therapeutic drug monitoring approaches, because measurement of systemic exposure after an initial oral dose will be less predictive of concentrations achieved with the next cycle of therapy. Nonlinear drug absorption is another pharmacokinetic variable that has the potential to significantly influence oral chemotherapy, and apparent saturation of drug absorption has been observed for oral methotrexate, etoposide, and leucovorin and may also exist for other anticancer agents (7–9). This has led to hyperfractionation approaches, whereby oral drug is administered multiple times a day rather than as one large daily dose, to achieve a greater overall daily systemic exposure. These factors do not preclude oral therapy, however, because oral mercaptopurine is a successful therapy, even with low bioavailability (~6%) and high interpatient pharmacokinetic variability (10, 11).
Patient compliance with prescribed drug therapy regimens is also an important variable that is of greatest concern when medications are self-administered, as is typically the case with oral chemotherapy. Inability of patients to successfully comply with a treatment regimen is thought to be a major source of therapy failure for many diseases. There is one school of thought that patient compliance will not be an issue with oral cancer therapy, because the seriousness of the disease will provide adequate motivation for adherence to the prescribed regimen. However, the few published studies on patient compliance with oral chemotherapy do not validate this assumption. A noncompliance rate of 43% was observed in breast cancer patients treated with an outpatient, oral cyclophosphamide regimen (12). Similarly, a full compliance rate of only 17% was noted in patients receiving oral allopurinol therapy for hematological malignancies (13). In addition, up to 10% of children receiving daily oral doses of mercaptopurine for childhood acute lymphoblastic leukemia had evidence for undercompliance of therapy during erythrocyte drug concentration monitoring (14).

There are a number of ways in which these important variables influencing oral chemotherapy can be addressed. One option is to ignore variability in drug absorption and problems with patient compliance of prescribed therapy. Although this strategy requires no time or effort on the part of the physicians, nurses, or pharmacists, it does come with the price that some patients may experience unnecessary toxicity, whereas others will be undertreated and possibly have a lower opportunity for therapeutic benefit, because of low systemic exposure to therapy (15). Alternatively, therapeutic drug monitoring can be performed, in which drug concentrations are measured in blood samples (most commonly plasma or erythrocytes) and these data used to individualize the patient’s dosage to achieve a target blood concentration. This strategy is widely used for a number of medications, including anticonvulsants, antibiotics, cardiovascular agents, and the anticancer agent methotrexate (6, 16). However, therapeutic drug monitoring does have the extra costs of nursing time for sample collection, assay for the drug of interest, and the need for knowledgeable interpretation of the drug concentration by the pharmacist or physician to implement the new therapy plan. A less expensive alternative to therapeutic drug monitoring is titration to toxicity (17). This approach has been used widely in the treatment of childhood acute lymphoblastic leukemia, under the assumption that the drug exposure necessary to achieve antitumor activity is similar to that which leads to significant but acceptable systemic toxicity (18). Great care would need to be used in implementing this strategy for drugs with schedule dependency, and this approach will not work for agents with a cytostatic mechanism of action (such as biological response modifiers, tyrosine kinase inhibitors, and others) or when therapy comprises multiple drugs with overlapping toxicities. Another potentially complementary strategy for reducing variability of oral chemotherapy is to minimize the sources of variability. For example, coadministration of enilunacl with 5-fluorouracil completely eliminates dihydrooriniidine dehydrogenase as a mechanism for pharmacokinetic variability (19), leading to enhanced and less variable oral bioavailability. Similar strategies have been used with paclitaxel and etoposide, in which inhibitors of small bowel and hepatic P-450 enzymes (ketoconazole) or both P-450 enzymes and P-glycoprotein (cyclosporin) have been administered to increase bioavailability (20, 21). Although these approaches do decrease variation in drug exposure after oral administration, they do not completely eliminate variability. Lastly, oral chemotherapy is only going to be effective if patient compliance can be optimized. Although this issue is not typically seen to be as exciting as biochemical modulation strategies or molecular characterization studies, it could have a large impact on therapeutic success for many regimens. It is imperative that efforts to ensure patient compliance be built into Phase III studies of oral chemotherapy if this method of drug administration is to reach its full potential in the treatment of human cancer.

References


